

A Short Note on Good Clinical Practice

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Abstract: Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and **reporting trials** that involve the participation of **human subjects** and was developed with consideration of the current good clinical standards of the European Union, Japan, and the United States, as well as those of Australia, **Canada**, the Nordic countries, and the World Health Organization (**WHO**). Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, and that the clinical trial data are credible. This standard should be followed when generating clinical trial data that are intended to be submitted to regulatory body (US Food and Drug Administration [**FDA**])

Key words: subject; clinical trial, ICHGCP guidelines; sponsor; FDA; investigator.

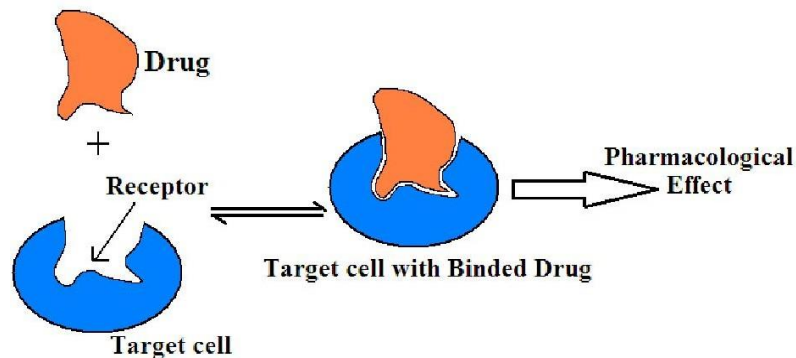
- **Pharmacodynamics:** What the drug does to the body.
- **Pharmacokinetics:** What the body does to the drugs.

What is a drug?

The drug is an exogenous non-nutritive chemical substance which when taken in the solid form by the mouth enter the **digestive tract** and there it is transformed into a solution and passed on to the **liver** where it is chemically altered and finally released into the **blood stream**. And in the blood it exists in two forms: **bound and unbound**. Depending on its specific affinity

for proteins in the blood (albumin, globulins), a proportion of the drug may become bound to plasma proteins, with the remainder being unbound. And since the **drug-protein binding** is reversible, the chemical equilibrium exists between the bound and unbound states, such that: **Protein + drug \leftrightarrow Protein-drug complex**. And the bloodstream carries the drug (free plus bound) to the **site of action**. Free drug reversibly bind to the target cell surface receptors. And the Bound drug slowly dissociates from the protein and binds reversibly to the target cell surface receptors to produce its **pharmacological effect**.

Drug + Receptor \leftrightarrow Drug - Receptor complex \rightarrow pharmacological effect



And the equilibrium constant for the formation of Drug - Receptor complex is given by:

$$K = [\text{Drug - Receptor complex}] / [\text{Drug}] [\text{Receptor}]$$

And K is a measure of how tightly a drug binds to the receptor: The higher the K value the drug bind well to the receptor, the action of the drug will be longer. In general, drugs with higher K values will require lower concentrations to achieve sufficient receptor occupancy to exert an effect. And after its **pharmacological effect** drug slowly detaches from the receptor. And then it is sent to the liver. And there it is transformed into a more water soluble compound called **metabolite** and released from the body through urine, sweat, saliva, and excretory products.

Agonists and Antagonists

Agonists: Drugs that have the ability to produce a **desired therapeutic effect** when bound to the target cell surface receptors.

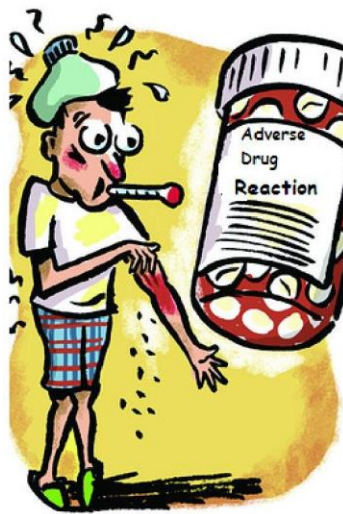
Antagonists: Drugs that bind well to the receptor but produce no therapeutic effect. They prevent other drugs from binding to the target cell surface receptors, thus they act as **blockers**.

Potency and Efficacy

Potency: The amount of a drug that is needed to produce a given effect.

Efficacy: The maximum effect that a drug can produce after binding to the receptor.

Adverse Event and Adverse Drug Reaction



Adverse Event: an injury, symptom, or disease temporally associated with the use of a medicinal drug, which **may or may not be related to the drug**.

Adverse Drug Reaction: an injury, symptom, or disease temporally associated with the use of a **medicinal drug**, which is related to the drug.

Serious Adverse Event

The **adverse event** is considered to be serious if it results in any of the following outcomes:

- Death.
- Prolonged or Long term **hospitalization**.
- Loss of consciousness, loss of speech, loss of memory and paralysis.
- **Birth defect:** Exposure to a medical product during pregnancy resulting in babies born with deformed arms and legs.
- Substantial risk of dying, **permanent change**, impairment, damage or disruption in function/structure, physical activities and/or quality of life.
- Internal bleeding with rapid drop in blood pressure, fatigue, a serious problem with breathing, prolonged diarrhea lasting more than 48 hours.

Expected and Unexpected Adverse Event

Expected Adverse Event: An adverse event is considered "**expected**" if it is listed in the investigator brochure or is listed in the Package Insert of a marketed drug.

Unexpected Adverse Event: An adverse event is considered "**unexpected**" if it is not listed in the investigator brochure or is not listed in the Package Insert of a **marketed drug**.

Clinical trail

Scientific investigation of safety and efficacy of medicinal products intended for human use.

ICH GCP guidelines / E6 guidelines



ICH: International Conference on Harmonization of technical requirements for registration of pharmaceuticals intended for human use.

GCP: Good clinical practice

1. An individual who participates in a clinical trial as a recipient of the **investigational product** is called a trial subject. And a scientifically sound clinical trial involving trial subjects should be conducted
 - in accordance with the ethical principles that have their origin in the **Declaration of Helsinki** (a statement of ethical principles to promote and safeguard the rights, safety, and well-being of the trial subjects) and in accordance with the international ethical and scientific quality standard and the applicable regulatory requirements.
 - in accordance with a clear, detailed **protocol** (A document that describes the objective, design and methodology to organize a trial) that has received prior **institutional review board** (IRB) or **independent ethics committee** (IEC) approval/favorable opinion.
2. The rights, safety, and **well-being** of the trial subjects should be safeguarded and clinical trial should be continued only if the **anticipated benefits** to the **foreseeable risks** ratio is far greater than 1.
 - anticipated benefits / foreseeable risks >1 (clinical trial is **continued**)
 - anticipated benefits / foreseeable risks < 1 (clinical trial is **terminated**)
3. Each individual involved in conducting a trial including
 - Investigator (a qualified physician or, when appropriate, a qualified dentist who is responsible for the conduct of the **clinical trial at a trial site** and / or to make important trial - related decisions) should be qualified by education, training, and experience to perform his or her respective tasks. And it is the responsibility of an **investigator** at a **trial site** (the location where trial-related activities are actually conducted) to give the medical care and to make **medical decisions** on behalf of trial subjects and to protect the privacy and confidentiality of personal information of trial subjects.
4. Freely given **informed consent** form should be signed, dated and obtained from every subject prior to his/ her willingness to participate in a particular trial.

- If a subject is unable to read the informed consent form, an **impartial witness** (a person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial) should be present to read the informed consent form and any other written information supplied to the subject.
5. **Investigational products** should be used, handled and stored in accordance with the approved **protocol** and in accordance with applicable regulatory requirements. Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects should be made with prior written **IRB/IEC** approval/favorable opinion.
 6. All clinical trial information including on clinical (Pharmacokinetics and investigational product **Metabolism**) and clinical information on an investigational product should be documented, handled, and **stored precisely** and it should be sufficient to support the proposed clinical trial. And systems with procedures that assure the quality of every aspect of the trial in compliance with **GCP** and the applicable regulatory requirements should be implemented.

Institutional Review Board / Independent Ethics Committee

An independent body constituted of medical, scientific, and **nonscientific members** whose responsibility is

1. To review a proposed trial within a reasonable time and give its

Approval/favorable opinion

Or

Disapproval/negative opinion

regarding the conduct of the trial at a trail site.

2. To conduct **continuing review of each ongoing trial** at intervals (at least once per year) to ensure

- The safeguard of the rights, safety, and well- being of **trial subjects** involved in a trial.
- The proper conduct of trial in compliance with **GCP** and the applicable regulatory requirements.

3. To review the protocol amendment and give its

Approval/favorable opinion

Or

Disapproval/negative opinion

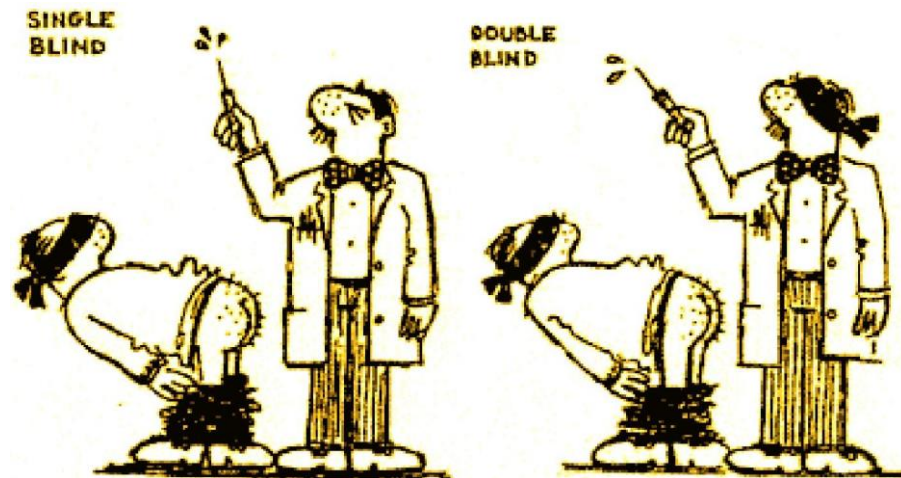
4. To review and ensure that information regarding payment to subjects for participating in the trial, including the methods, amounts, and schedule of **payment** to trial subjects prorated in the written informed consent form.
5. To ensure the proper payments and **compensation** available to subjects.
6. To obtain the following documents:
 - Signed and dated informed consent forms.
 - **Investigator's Brochure (IB)**:A complete collection of the clinical and nonclinical information regarding the clinical study of the investigational product in trial subjects.
 - **Investigator's current curriculum** vitae and/or other documentation evidencing his/ her qualifications.
 - Information about payments and compensation available to subjects.
 - Protocol and protocol amendments.
 - Subject recruitment procedures and advertisements.
 - Other clinical trial-related information.

And retain for a period of at least 3 years after completion of the trial and make them available upon request from the sponsor and/ or the **regulatory bodies** (US Food and Drug Administration [FDA]).

Blinding/masking

A procedure in which one or more persons related to the trial are kept unaware of the treatment strategies.

- **Single blinding:** only subject is kept unaware of the treatment strategies.
- **Double blinding:** subject, investigator, monitor, and, in some cases, **data analyst** are kept unaware of the treatment strategies.



If the **trial is blinded**, the investigator should promptly document and explain to the **sponsor** any premature violation of blinding due to serious adverse event or in the case of medical emergency to find out whether a particular subject received the investigational product, or received a **comparator** (marketed product or placebo).

Phases of Clinical trail

- **Preclinical research:** In this phase, researchers test the investigational product in the laboratory or in animals before it can be tested in humans. Preclinical results frame the basis for applying an **investigational new drug (IND)** application to the **Food and Drug Administration (FDA)** to seek permission to use the investigational product in a **Phase I** trial.
- **Phase I:** In this phase, the investigational product is tested in a 20 to 100 of healthy volunteers who are not at risk for disease to determine the safety and a safe **dosage** range

(maximum concentration of the investigational product above which the investigational product can produce harmful effects in the body), and identify side effects.

- **Phase II:** In this phase, the investigational product is tested in a 20 to 300 of unhealthy volunteers with the disease to determine the efficacy [how well the **investigational product** works compared to a comparator (marketed product or **placebo**)]. (**Placebo**: a substance that has no **therapeutic effect** but used as a control in testing investigational product).
- **Phase III:** In this phase, the investigational product is tested in a 1,000 - 3,000 unhealthy volunteers with the disease (at multiple centers) to confirm the safety, efficacy and side effects of the investigational product. This is the final phase prior to seek marketing approval (or to apply an **new drug (ND) application** to the **Food and Drug Administration (FDA)** to seek permission to market the product confirming that the investigational product is safe, effective, have **anticipated benefits** that outweigh the foreseeable risks, producible in a consistent quality and purity).
- **Phase IV:** post marketing surveillance to understand the risks, benefits, and optimal use of the marketed product.

In order to protect the welfare and well-being of animals used in preclinical studies, the preclinical research is guided by 3 principles:

1. Reduce the number of usage of **animals** to a minimum.
2. Replace animal experiments with alternative **non-animal experiments** wherever possible.
3. Design the experiment in such a way that the adverse effect on the animal is minimized and its welfare is improved.

Investigator

A qualified physician or, when appropriate, a **qualified dentist** whose responsibility is

- To recruit the required number of suitable subjects and inform them about the trial and take their **voluntary consent** towards the participation in the trial.

- To recruit an adequate number of qualified staff and adequately inform them about the protocol, the investigational product, and their **trial-related duties and functions**.
- To conduct the trial properly and safely in compliance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the **Declaration of Helsinki** within the agreed trial period and use, handle and store the investigational product as described in the protocol.
- To give the adequate medical care to a subject in the case of any medical emergency or serious adverse events (or serious adverse drug reactions) and report the expected and unexpected serious adverse events (or **serious adverse drug reactions**) to the regulatory body and the IRB/IEC and the sponsor.
- To inform the subject about the correct use of the investigational product and check at intervals that each **subject** is following the instructions properly.
- To provide the accurate, liable, complete **clinical and non-clinical trial** related documents for review upon request from the IRB/IEC and/ or the regulatory bodies.
- To retain the entire trial related essential documents including medical documents and a summary of the trial's outcome for a period of **at least 2 years after completion of the trial** and make them available upon request from the sponsor and/ or the regulatory bodies.
- To complete the trial within the agreed trial period.
- To safeguard the rights, safety and **well-being of the subject** involved in the trial.
- Not to implement any deviation from, or changes of, the protocol without prior review and documented approval/favorable opinion from the IRB/IEC. If the any deviation from, or changes of, the **protocol is approved from the IRB/IEC**, then it should be documented with proper explanation.
- To allow the **audit** (systematic and independent examination of trial-related activities and documents to determine whether the **trial-related activities** are conducted, recorded and accurately reported according to the protocol, sponsor's standard operating procedure (SOP: Detailed written instructions to perform a specific function), good clinical practice (GCP) and the applicable **regulatory requirements**).

Vulnerable subjects



- Patients in emergency situations with **incurable** diseases.
- Homeless, unemployed and impoverished persons.
- Mentally challenged persons who are incapable of giving informed consent.
- Prisoners, medical, pharmacy, dental, and nursing students.
- Nomads, refugees.
- Children, **pregnant** women, **Fetuses**.
- Addicts, sexual minorities.

Investigator should give **adequate justification for the use of vulnerable subjects** and special attention should be paid to trials that involve vulnerable subjects.

Sponsor

An organization, institution, or an individual whose responsibility is

- To initiate, manage and finance the trail (including the costs of **treatment of trial subjects** in the case of **medical emergency** or serious adverse events).
- To implement systems with procedures that assures the quality of every aspect of the trial in compliance with the **protocol**, **GCP** and the **applicable regulatory requirements**.
- To designate a **qualified medical expertise professional** who will be readily available to give suggestions on trial-related medical problems.
- To employ qualified **biostatisticians**, clinical pharmacologists, and **physicians** to design the protocol and **CRF (case report form)** and plans to conduct, handle, manage,

organize the trial and document the clinical study information in compliance with GCP and the applicable regulatory requirements.

- To employ qualified individuals and establish an Independent **Data Monitoring Committee** to supervise the overall conduct of the trial, verify the data, conduct the statistical analyses at intervals to ensure that the trial is conducted in **compliance** with the protocol, **SOP**, GCP and the **applicable regulatory requirements**.
- To retain all the **essential documents** for a period of at least 2 years after completion of the trial and make them available upon request from the regulatory bodies.
- To select the **qualified investigators and institutions** those have adequate resources to properly conduct the trial in compliance with the **approved protocol**, SOP, GCP and the applicable regulatory requirements.
- To define, establish and designate all the trial related teams (including monitoring, **pharmacovigilance**, safety and data management team) to document and manage the trial.
- To supply the investigator / trial site with the **investigational product** and with the information how to use, handle and store the investigational product.
- To report all the concerned information about adverse drug reactions (**ADRs**) those are both **serious and unexpected** to the regulatory bodies and/ or to the IRB/IEC.
- To dispose and document the **unused** investigational product.

If the sponsor discontinues the trial, the sponsor should maintain all specific essential documents for at least 2 years after **formal discontinuation** of the trial.

Clinical research coordinator (CRC)

Person whose responsibility is

- To handle most of the **administrative responsibilities** of a clinical trial on behalf of an investigator and manage the collection of **data** throughout the course of a clinical trial.
- To assist the principal investigator with preparation of CRF (**Case Report Form**: a tool used by the sponsor of the clinical trial to collect data from each participating trial site as

defined by **protocol**), monitoring, **quality assurance**, audits, and data management and analysis.

- To manage subject's information and **medical care**.

CRC should perform all the duties under the **supervision of investigator** in compliance with good clinical practice (**GCP**) and the applicable regulatory requirements.

Clinical research associate (CRA)

Person employed by a sponsor whose responsibility is

- To monitor the **progress of a clinical trial** at a trial site.
- To ensure the **safeguard of rights**, safety and well-being of trial subjects.
- To supervise the overall conduct of the **trial**, verify the data, conduct the **statistical analyses** at intervals to ensure that the trial is conducted in compliance with the protocol, **SOP**, **GCP** and the applicable regulatory requirements and **adverse events** are correctly **documented** and reported.

Dose: The amount of drug **prescribed** to be taken at one time.

Dosage: The amount of drug to be taken.

Dosage form: means by which the drug reach the **target cell** to give its actions.

Labeling / unblinding

A **procedure** in which both the investigator and **trial subject** is kept aware of the treatment strategies.

Randomization

The process of assigning **trial subjects** to treatment or control groups using an element of chance in order to reduce **bias**.

Nuremberg code (1947)

During the **Nuremberg War Crimes Trials**, 23 **German doctors** were charged with **crimes** against humanity for "performing **medical experiments upon prisoners** and other living human subjects, **without their consent**, in the course of which experiments they committed the murders, brutalities, cruelties, tortures, and **other inhuman acts**." As part of the verdict, the Court enforced some rules for "**Permissible Medical Experiments**", now known as the "**Nuremberg Code**".

These rules include:

- Voluntary consent.
- Anticipated benefits should **outweigh** foreseeable risks.
- Ability of the subject to **terminate** participation.

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